REMARKS

Pursuant to the formal interview with Examiner Moser on June 8, 2000 and informal telephone discussions with Examiner Portner, Applicants have amended the claims as indicated above. Specifically, Applicants have amended claims 8-10 as suggested by Examiner Moser and claims 1 and 6 has suggested by Examiner Portner in order to clarify the intent of the claims. In addition, the claimed invention has been defined as being an assay for the detection of proteins. With this amendment the invention is further distinguished from the prior art which is largely drawn to assays and methods for detecting nucleic acids.

Each of the specific rejections of the final Office Action of November 19, 1999 is specifically addressed below.

Rejections under 35 U.S.C.§112, first paragraph and second paragraphs

Claims 6, and 8-10 have been rejected under 35 U.S.C.§112, first paragraph for lack of enablement. Specifically, the Examiner asserts that claims 6, and 8-10 fail to recite essential ingredients. Claims 8-10 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. More specifically, claims 8-10 have been rejected for failing to recite essential reagents. Independent claim 6 has been

amended to recite that the conjugation of the oligonucleotides takes place through

i) hybridization of an oligonucleotide complementary to the conjugatable oligonucleotides;

ii) hybridization of the conjugatable oligonucleotides to each other; or

iii) ligation of the oligonucleotides.

As such the meaning of conjugation has been fully and clearly defined and all necessary reagents have been defined in the claims. Withdrawal of the rejections is, therefore respectfully requested.

Rejections under 35 U.S.C.§102(e) and 103

The Examiner maintains the rejection of claims 1-6 and 8 and 1-4 under 35 U.S.C. §103 as being obvious over Lee et al. in view of Dattagupta and Ciechanover et al. In the informal telephone discussion with Examiner Portner it was indicated by the Examiner that she believed Ciechanover et al. to be the nearest cited reference to the invention.

Applicants acknowledge that Lee et al. discloses the use of multiple antibodies to different epitopes on an antigen. However, as clearly shown in Figures 5 and 6 of Lee et al. there is no need for the antibodies to the bind in close proximity on the target antigen to

create a signal. In fact, as shown in Figures 5 and 6 the antibodies can bind on fully opposite sites of the target antigen. With Lee et al. none of the affinity reagents are actually interacting with each other directly to produce a signal. Thus, Lee et al. fail to teach signal production only when the second and third affinity reagents (antibodies) are closely bound on the same macromolecule. Dattagupta et al. and Ciechanover et al. pertain to the use of nucleic acid probes and amplification of a signal by using nucleic acid probes. However, neither Dattagupta et al. nor Ciechanover et al. teach that amplification (signal) only occurs if two separate affinity reagents are closely bound on the same target macromolecule.

The cited portion of Ciechanover et al. relied on by the Examiner (column 5,384,255, lines 46-68) indicates that the antibodies which recognize E2-F1 can be detectably labeled with DNA using PCR. However, there is no disclosure in Ciechanover et al. of the use of two antibodies that bind to two different determinants on the E2-F1 molecule to generate a signal only through the interaction of the oligonucleotides on the two antibodies. Column 19, line 65 through column 20, line 3, refers to a '"ligase chain reaction" in which two (or more) oligonucleotides are ligated in the prescence of a nucleotide target....' However, the ligase chain reaction of Ciechanover et al. is not ligating nucleotide sequences on two separate antibodies, but is

a means of amplifying a signal by ligating two probes which bind to the nucleic acid tag on a single antibody. See Figure A, below for an illustration.

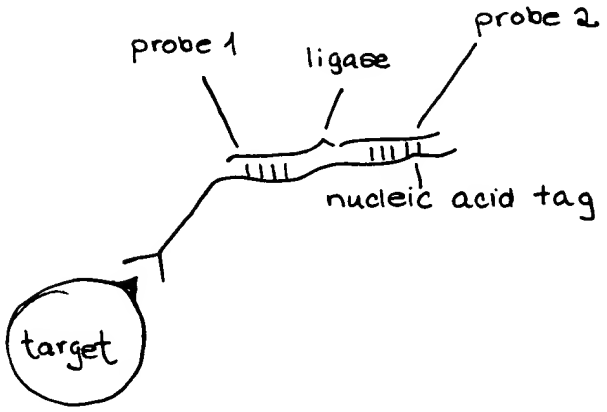

Figure A - ligase chain reaction of Ciechanover et al.

In reading further from the disclosure of Ciechanover et al. regarding the use of a "PCR-immunoassays", which include the "ligase chain reaction," the use of two different antibodies which bind to two different determinants was clearly not only not contemplated, it is precluded by Ciechanover et al. Column 20, lines 4-31 provide a detailed discussion of how an "immuno-PCR" assay of Cienchanover et al. is conducted. Column 20, lines 7-8, specifically state that the wells are incubated with a monoclonal antibody. If a single monoclonal antibody is used, the assay method excludes the use of two different antibodies which recognize two different determinants. Only a single determinant is being recognized in the assay of Ciechanover et al. As

such, it is not possible to achieve the present invention by combining the disclosure of Cienchanover with that of Lee et al. and Dattagupta.

As such, Dattagupta et al. and Ciechanover et al. fail to overcome the deficiencies of Lee et al. and the present invention is not achieved by combining the references. Withdrawal of the rejection is therefore respectfully requested.

The Examiner maintains the rejection of claims 1 and 3-5 under 35 U.S.C. §§102 or 103 (as indicated) over either Birkenmeyer et al., Nickerson et al., Delahunty et al., Kwok et al. and Nilsson et al.

With regard to Birkenmeyer et al., the Examiner appears to be interpreting the amplification of the DNA as inherently meeting the present feature of only obtaining a signal when the second and third affinity reagents are closely bound on the same macromolecule.

With regard to Kwok et al., Nickerson et al. and Nilsson et al., the Examiner asserts that these references teach probes which will only generate a signal if two affinity reagents are bound sufficiently close to each other.

Applicants traverse these rejections and withdrawal thereof is respectfully requested. As indicated in the Abstracts of each of the cited references, Birkenmeyer et al., Nickerson et al., Delahunty et al., Kwok et al. and Nilsson et al. all pertain to the detection of nucleic acid sequences, i.e. with all of these references nucleic

acid sequences are the target molecules, not the probes. The nucleic acids in all of these references are the "specific macromolecule" of claim 1 and the "specific antigen" of claim 6. In these references, it is the target molecule which is being amplified, not the probe molecule. There is no suggestion in these references of using two probe molecules (affinity reagents) which will generate a signal by nucleic acid amplification only if the second and third probe molecules are closely bound to the target macromolecule. As such, there is no disclosure or suggestion in Birkenmeyer et al., Nickerson et al., Delahunty et al., Kwok et al. or Nilsson et al. of the present invention and the present invention is therefore not obvious over these references.

Finally, claims 1-4 remain rejected under 35 U.S.C.§103 as being obvious over Hendrickson et al. Hendrickson et al. discloses a "multianalyte immunoassay" for detecting three different analytes. See Abstract. The immunoassay of Hendrickson et al. uses nucleic acid conjugated antibodies as probes. However, Hendrickson et al. fails to teach the feature of the present invention that amplification of the nucleic acid probes only takes place and thus signal is only generated if two different antibodies are sufficiently closely bound to the same target antigen.

By requiring the binding of two different affinity reagents in sufficiently close proximity to one another before signal will be generated, the present invention renders most non-specifically bound affinity reagents incapable of generating a signal because most non-specific binding will be at a distance too great to initiate amplification. There is no disclosure or suggestion in Hendrickson et al. of this feature of the present invention or the advantages associated therewith. As such, the present invention is not obvious over Hendrickson et al.

As the above-presented amendments and remarks in no way add new matter or raise new issues for consideration and further address and overcome the rejections of the Examiner, reconsideration and allowance of the claims are respectfully requested. Should the Examiner have any questions regarding the present application, she is requested to contact MaryAnne Armstrong, PhD (Reg. No. 40,069) in the Washington DC area, at (703) 205-8000.

Pursuant to 37 C.F.R. §§1.17 and 1.136(a), Applicants respectfully petition for an additional three (3) months extension of time for filing a response in connection with the present application, two months having been previously been petitioned, and the required fee of $755.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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